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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/603,885	06/26/2000	Stephen William Watson Michnick	Oddy 004	2144

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EXAMINER
PONNALURI, PADMASHRI

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 12/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/603,885	Applicant(s) Michnick et al
	Examiner Padmashri Ponnaluri	Art Unit 1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 16, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above, claim(s) *2, 5-8, and 10-17* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3, 4, and 9* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

NOTE: The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1639.

1. This application claims priority to a provisional application 60/141210, filed on 6/26/99.

2. Claims 1-17 are currently pending in this application.

3. Applicant's election with traverse of Group I, claims 1, 3-4 and 9, in Paper No. 11, filed on 9/16/02 is acknowledged. The traversal is on the ground(s) that the invention strategy is based on the folding of the murine enzyme DHFR from complementary fragments; and the restriction into nine groups does not appear reasonable given the total number of claims; and applicants believe that there is unity of invention as required by MPEP 800. This is not found persuasive because the instant claims do not recite that the methods or the products are based on mDHFR as in the applicants arguments; and the restriction of the claims is based on the independent and distinct inventions claimed and not on the number of claims present; and further applicants argue that there is unity of invention as required by MPEP 800, is not persuasive because this application is not an international application in which unity of invention is present; and further the search between the groups would be burdensome because inventions of different groups would require completely different searches in non-patent databases, and there is no

exception that the searches would be co-extensive. Therefore, these do not create an undo search burden, and restriction for examination purposes as indicated is proper.

The requirement is still deemed proper and is therefore made FINAL.

4. Applicant's election without traverse of the following species: enzyme mDHFR as reporter molecule; enzymatic activity as detectable activity; WinZip A1 proteins as first panel of molecules; WinZip B1 as second panel of molecules; peptides or proteins as a library of molecules, in Paper No. 11 is acknowledged.

5. Claims 2, 5-8, 10-17 are withdrawn from further consideration pursuant to 37 CAR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11, filed on 9/16/02.

6. Claims 1, 3-4 and 9 are currently being examined in this application.

7. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CAR 1.78(a)(2) and (a)(5)).

8. Applicant is invited to notice that boxes 10, and 12 were checked by the draftsman. If applicants renumber the figures, applicant is encouraged to amend the specification so that the description of renumbered figures corresponds to the renumbered figures.

9. The listing of references in the specification is not a proper information disclosure statement. 37 CAR 1.98(b) requires a list of all patents, publications, or other information

submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

10. Claim 9 is objected to because of the following informalities: 'a method according to any of the claims 1-8', which is dependent on non elected claims.. Appropriate correction is required.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1, 3-4 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for dihydrofolate reductase (DHFR) as reporter molecule and the use of leucine zipper molecules as panel of molecules in the method of identifying an interacting set of molecules, does not reasonably provide enablement for use of any other reporter molecule and other molecules in the claimed method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims recite a method for identifying an interacting set of molecules comprising: generating fragments of a reporter molecule; coupling first fragments to members of a first panel of molecules; coupling second fragments to members of second panel o molecules; mixing the products; testing for activity; identifying the panel members whose interaction resulted in said activity and which would form interacting set.

The specification discloses a library versus library screening in intact cells based on the folding of murine enzyme DHFR. The specification discloses that the method is useful in investigating selection of dimerizing leucine zipper pairs from two designed semi-randomized libraries. The disclosure does not teach the use of any other enzymes or interacting panel members commensurate in scope with the claimed method, which may include any type of reporter and library of panel of molecules. The claimed method does not appear to be within the scope of reasonable experimentation.

The factors to be considered in a determination of undue experimentation are set forth in *In re Wands,* (U.S.P.Q. 2d 1400 (CAFC 1988). The factors to be considered include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the predictability of the art and the breadth of the claims.

1) The specification fails to give adequate direction and guidance for use of any other enzyme molecules and library members in the claimed method. The specification uses mDHFR as reporter enzyme, which is relatively small and monomeric and structural and functional information of the DHFR and as well as interaction with the leucine Zipper protein is well known in the art. The specification does not sufficiently teach how to choose the enzyme and the library of molecules to practice the claimed method. The specification only teaches that the panel of molecules are randomized libraries of leucine zipper pair. The specification does not teach the use of two different panel of molecules which are not related structurally or functionally.

In light of the foregoing, the specification does not sufficiently teach the claimed methods for identifying interacting set of molecules.

2) The specification fails to provide working examples of the preparation of libraries or panels of molecules other than the leucine zipper pairs. The specification examples are drawn to the use of mDHFR fragments and randomized leucine zipper pair molecules as panel of molecules in the method of identifying interaction between the molecules. However, the instant claimed method recites the use of fragments of any reporter molecule which has detectable activity when associated, and two panels of molecules.

3) The breadth of the claims encompasses use of any number of reporter compounds and libraries as interacting set. The claims encompass the use numerous reporter molecules , however the specification no where discloses the relationship between the reporter molecules and the panel members. That is from the specification disclosure of the use of mDHFR as reporter and leucine zipper molecules as panel of molecules, it is clear that the reporter and the panel of molecules are known to have some kind of interactions or related. However, the breadth of the claims encompasses the use of any reporter molecules and panel members in the method, whose relationship is not addressed by the specification.

4) The state of the prior art is such that library v library screening methods are not well known at the time the invention was made. The specification discloses the claimed method of screening library versus library using different libraries which are based upon a known compound (single compound pair) and the enzyme is known to interact with the libraries compounds claimed.

However, the enzyme (DHFR)or the libraries (random libraries of leucine zipper pair) neither encompass the breadth of the claimed subject matter, nor do they provide enabling method for the scope of the methods now claimed..

5) The art is inherently unpredictable, because it is not possible to predict with any certainty how to screen the libraries versus libraries without knowing the reaction between the enzyme or the libraries screened.

Based upon the foregoing, it is concluded that an undue experimental burden is involved in method of identifying interacting set of molecules, the full scope of the claimed invention.

Therefore, while it is true that the level of skill in the art is high, it would require undue experimentation to conduct the methods now claimed in the absence of guidance.

13.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1, 3-4 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites 'first fragments', 'second fragments', which are not clear does applicants mean the fragments of the reporter molecules or any other molecules. And further it is not clear what constitutes first fragments and second fragments. Applicants are requested to amend the claim to clearly recite the first fragments and second fragments.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: the structural and functional association between the reporter enzyme and the panel of molecules .

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: method steps involving the testing for activity. The claims does not include how the activity is tested.

Claims 3, 4 recite the limitation "said panels" . There is insufficient antecedent basis for this limitation in the claim or in the independent claim 1.

Claim 4 recites 'at least two of said panels', it is not clear what does applicants mean by 'at least two of said panels', since claim 1 recites the use of 'first panel and second panel'. Applicants are requested to clarify.

Claim 9 recites a reference set of fragments, however the metes and bounds of the 'reference fragments' is not clear. Which fragments are considered as reference fragments. Applicants are requested to clarify.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1, 3-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Pelletier et al (Protein Engineering, 1997, vol. ~~89~~ 10, page 89).

Pelletier et al disclose a protein complementation assay for detection of protein-protein interaction in vivo. The reference discloses a protein complementation assay based on reconstitution of DHFR activity. The reference discloses that the direct assay disclosed requires no additional endogenous factors for detecting specific protein-protein interactions. The reference discloses that DHFR is used as reporter enzyme, and GCN4 leucine zippers as model interacting proteins because of their association is well characterized. The reference in figure 1 discloses that the fragments of reporter molecules interaction with leucine zipper proteins. The reference discloses that the method is useful in identifying protein-protein interactions. The reference specifically teaches that the method is applicable to screening cDNA libraries for the detection of unknown, specific protein-protein interactions. Thus, the reference clearly anticipates the claimed invention.

17. (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

18. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

19. Claims 1, 3-4 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 6,270,964 (Michnick et al).

Michnick et al disclose protein fragment complementaion assay for the interaction of biological or drug interactions. The reference discloses that the assay can be used to screen cDNA libraries for binding of a target protein with unknown proteins or libraries of small organic molecules for biological activity. Figure 1 in the reference depicts the protein complementation assay. Figure 7 in the reference discloses the method of library versus library screening as the instant claimed method. The reference discloses two semi-random leucine zipper libraries were created and each inserted N-terminal to one of the mDHFR fragments. The reference discloses that the cotrasformation of the resulting zipper-DHFR fragments libraries in E.coli and platting on selective medium allowed for survival of clones harboring successful interacting leucine zippers. Fourteen clones were isolated and the zippers were sequenced to identify the residues at "e" and "g" positions. The "e-g" pairs were categorized as attractive pair and repulsive pair (see column 9, lines 35 to 47). Example 7 of the reference further diploses the application of the PCA strategy to generate peptides with novel binding properties that may have therapeutic value using

two leucine zipper libraries and fragments of mDHFR. Thus the reference clearly anticipates the claimed invention.

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 U. S. P. Q. 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 U. S. P. Q. 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 U. S. P. Q. 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 U. S. P. Q. 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CAR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CAR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CAR 3.73(b).

21. Claims 1, 3-4 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-41 of U.S. Patent No. 6,270964. Although the conflicting claims are not identical, they are not patentably distinct from each other because the reference claims recite protein fragment complementation assays for detection of molecular

interactions and the compositions. The claimed method of identifying interacting set of molecules is obvious in view of the reference claimed protein complementation assay because the reference recite same method steps. The claimed method differs from the reference claimed method by reciting panel of molecules or library of molecules. The reference claims recite that the fragments of the enzyme are fused to other molecules which would read on the library or panel of molecules.

22. No claims are allowed.

23. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to P. Ponnaluri whose telephone number is (703) 305-3884. The examiner is on ***Increased Flex Schedule*** and can normally be reached on Monday to Friday from 7.00 AM to 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

P. Ponnaluri
Patent Examiner
Technology Center 1600
Art Unit 1639
02 December 2002

PADMASHRI PONNALURI
PRIMARY EXAMINER